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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/506,763	05/12/2005	Heinz Peter Vollmers	043043-0358749	8912

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EXAMINER	
HALVORSON, MARK	

ART UNIT	PAPER NUMBER
1642	

NOTIFICATION DATE	DELIVERY MODE
07/09/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Office Action Summary	Application No.	Applicant(s)	
	10/506,763	VOLLMERS ET AL.	
	Examiner	Art Unit	
	Mark Halvorson	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *4/16/2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,7-9,11-16 and 54-78* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,7-9,12-16 and 54-78* is/are rejected.

7)☒ Claim(s) *11* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submissions filed on September 19, 2007 has been entered.

Claims 1, 2, 4 , 7-9, 11-16 and 54-78 are pending and under examination.

35 USC § 112 1st paragraph rejection withdrawn

Upon review and reconsideration and Applicants comments the rejection of claim 11 under 35 USC 112 for failing to comply with the enablement requirement is withdrawn.

35 USC § 112 1st paragraph rejection maintained

Claims 1, 2, 4 , 7-9, 12-16 and 54-65 remain rejected and new claims 66-78 are rejected for failing to comply with the enablement requirement.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4 , 7-9, 12-16 and 54-78 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody or an antigen-binding fragment thereof that binds to binds to at least one of HT-29, CACO-2, COLO-320, COLO-206F, or COLO-678, the antibody or antigen binding fragment

comprising the heavy chain variable region sequence of SEQ ID NOs:1 and the light chain variable region sequence of SEQ ID NOs: 3 is not enabling for an antibody or functional fragment thereof that binds to binds to at least one of HT-29, CACO-2, COLO-320, COLO-206F, or COLO-678, the antibody or antigen binding fragment comprising a heavy chain variable region sequence with 75%, 80%, 85%, 90% or 95% identity to SEQ ID NO:1 and a light chain variable region sequence with 75%, 80%, 85%, 90% or 95% identity to SEQ ID NO:3 SEQ ID NOs: 3, wherein the heavy chain or light chain variable region sequence has an insertion or deletion of one amino acid residue. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The claims as amended teach isolated antibodies or functional fragments comprising the amino acid sequence with 75%, 80%, 85%, 90% or 95% identity to SEQ ID NO:1 and/or the amino acid sequence with 75%, 80%, 85%, 90% or 95% identity to SEQ ID NO:3. In addition, the claims teach purified peptides comprising the amino acid sequence of SEQ ID NO:1 or the amino acid sequence of SEQ ID NO:3. The claims also teach a purified antibody comprising the amino acid sequence of SEQ ID NO:1 and the amino acid sequence of SEQ ID NO:3 wherein one of he amino acid sequences has an insertion or deletion of one amino acid residue.

The specification discloses an IgM antibody, CM-1, that induces apoptosis of a neoplastic cell but does not induce apoptosis of a non-neoplastic cell wherein the antibody specifically binds to at least one of HT-29, CACO-2, COLO-320, COLO-206F, or COLO-678 cells, the antibody comprising a heavy chain variable region consisting of the amino acid sequence of SEQ ID NO: 1, and a light chain variable region consisting of SEQ ID NO:3. Thus, neither the epitope nor even the specific antigen bound by the claimed antibody is disclosed. The specification further discloses that a functional fragment has an amino acid sequence that is substantially identical to a fragment, e.g., 5, 10, 15, 20, 15, 30, 50, 75, or 100 contiguous amino acids, of the amino acid sequence of SEQ ID NO:1 or 3.

Applicants argue that in view of the guidance in the specification and knowledge in the art regarding antibody structure and function at the time of the invention, and that antibody variants and functional fragments having the requisite activity could be produced and identified using routine methods disclosed in the specification or that were known in the art at the time of the invention, one skilled in the art could make and use the claimed antibodies and functional fragments comprising a sequence at least 75% identical to the amino acid sequence of SEQ ID NO: 1 (e.g., 8O%, 85%, 90%, 95%, etc.), and a sequence at least 75% identical to the amino acid sequence of SEQ ID NO:3 (e.g., 8O%, 85%, 90%, 95%, etc.), and heavy and light chain sequences of SEQ ID NO: 1 and SEQ ID NO:3, without undue experimentation. Applicants argue that because the level of knowledge in the art with respect to antibody structure and function was high at the time of the invention, such as the sequences that contribute to antigen binding of antibodies (e.g., CDRs and FRs), the skilled artisan would know residues of SEQ ID NO: 1 and SEQ ID NO:3 that would be amenable to substitution and would therefore be able to predict with reasonable certainty antibody variants of SEQ ID NO:1 and SEQ ID NO:3 that would have at least partial cell binding activity. Applicants also cite *In re Wands* and point out that if the skilled artisan wished to produce antibody variants and functional fragments, producing recombinant proteins was routine in the art at the time of the invention, and the specification discloses routine assays for identifying antibodies that bind to the recited cell types, as well as cell proliferation/apoptosis assays. In addition, Applicants argue that the number of antibody variants and functional fragments encompassed by claims 1, 2, 4, 7 to 9, 11 to 16 and 54 to 78 are limited as they are required to have at least some degree of binding to the recited cell lines and therefore do not include inoperative embodiments. Applicants argue that the antibodies and functional fragments are further limited in number because of the high degree of sequence identity among members, namely they have a sequence at least 75% identical to the amino acid sequence of SEQ ID NO: 1 and a sequence at least 75% identical to the amino acid sequence of SEQ ID NO:3.

Applicants further argue that claims 64 and 65 are adequately enabled under 35 U.S.C. $1 12, first paragraph, regardless of whether SEQ ID NO:1 or SEQ ID NO:3

binds antigen. Applicants argue that each of SEQ ID NO: 1 and SEQ ID NO:3 could be linked in order to form small antigen binding fragments (see, page 18, lines 4-9). In addition, each of SEQ ID NO: 1 and SEQ ID NO:3 could be expressed in a eukaryotic or prokaryotic cell line in order to produce an antibody that contains SEQ ID NO: 1 and SEQ ID NO:3 without undue experimentation, as disclosed in the specification.

Applicants have submitted a Declaration under 37 C.F.R. *5* 1.132 executed by Dr. Peter Vollmers and argue that the Declaration corroborates Applicants' position that the claims are adequately enabled under 35 U.S.C. *5* 1 12, first paragraph. The Declaration discloses that antibodies and functional fragments could be produced in view of the guidance in the specification and knowledge in the art as exemplified by Liddell and Cryer at the time of the invention. The Declaration further discloses that methods of identifying antibody variants that have binding activity without undue experimentation were also known in the art as exemplified by Liddell and Cryer and are also disclosed by the specification. The Declaration further cites Kipriyanov et al, Holmes et al and Lantto et al as indicating the state of the art for producing functional antibodies by insertions and deletions.

Applicants arguments have been considered but are not persuasive. It is important to note that the instant specification discloses and teaches one antibody comprising a heavy chain variable region consisting of the amino acid sequence of SEQ ID NO: 1, and a light chain variable region consisting of SEQ ID NO:3. The instant specification does not disclose or teach a single antibody variant comprising a VH domain and a VL domain whose amino acid sequences are at least 75%, 80%, 85%, 90% or 95% identical to the respective VH and VL domains of the claimed antibody. Furthermore, the claims are drawn to an antibody that specifically binds to at least one of HT-29, CACO-2, COLO-320, COLO-206F, or COLO-678 cells. It is also important to note that the epitope recognized by the claimed antibody is not disclosed. Thus, it is inferred that the actual epitope recognized by the claimed antibody is not known. Since all that is necessary is that the variant antibody binds to binds to at least one of HT-29, CACO-2, COLO-320, COLO-206F, or COLO-678 cells, it would not be known whether the variant antibody is binding the same epitope as the antibody comprising a

heavy chain variable region consisting of the amino acid sequence of SEQ ID NO: 1, and a light chain variable region consisting of SEQ ID NO:3. Thus, the present claims are drawn to antibody variants, which are not disclosed or taught, but as asserted by applicant could be produced using any one of the antibody engineering techniques disclosed in the specification or taught in the art which may not even bind the same epitope as the antibody comprising a heavy chain variable region consisting of the amino acid sequence of SEQ ID NO: 1, and a light chain variable region consisting of SEQ ID NO:3. This does not constitute adequate enablement.

The art cited by applicant as well as the instant specification disclose techniques/protocols for amino acid substitutions, deletions and/or insertions demonstrate that there are numerous modifications and multiple approaches for one skilled in the art to begin experimenting to discover the nature, extent and general tolerance of modifications in the heavy and light chains to determine which technique best for producing variant antibodies. The instant specification does not provide the skilled artisan with a starting point or direction in which to begin experimentation, nor does it provide exemplary guidance which is reasonably predictive for producing antibody variants comprising a VH domain and a VL domain whose amino acid sequences are at least 75%, 80%, 85%, 90% or 95% identical to the respective VH and VL domains of the claimed antibody, as embraced by the claims. In essence, Applicant claims an invention, not yet discovered and essentially calls for trial and error by the skilled artisan using techniques disclosed in the specification or taught in the art to begin discovering the claimed invention without assisting the skilled artisan in such an endeavor, which is insufficient to constitute adequate enablement.

In regards to Applicants assertion that claims 64 and 65 are adequately enabled under 35 U.S.C. $1 12, first paragraph, regardless of whether SEQ ID NO:1 or SEQ ID NO:3 binds antigen. Applicants argue that each of SEQ ID NO: 1 and SEQ ID NO:3 could be linked in order to form small antigen binding fragments. In addition, Applicants argue that each of SEQ ID NO: 1 and SEQ ID NO:3 could be expressed in a eukaryotic or prokaryotic cell line in order to produce an antibody that contains SEQ ID NO: 1 and SEQ ID NO:3 without undue experimentation, as disclosed in the specification. The

claims are drawn to a single chain polypeptides comprising either the amino acid sequence of SEQ ID NO:1 or the amino acid sequence of SEQ ID NO:3 not a polypeptide comprising both the amino acid sequence of SEQ ID NO:1 and the amino acid sequence of SEQ ID NO:3. One would not know how to use the single chain polypeptides comprising either the amino acid sequence of SEQ ID NO:1 or the amino acid sequence of SEQ ID NO:3 because it has not been demonstrated that either of these single chains bind antigen and it is likely that neither of these chains would bind antigen.

The specification does not provide sufficient guidance or direction as to the general tolerance to modification and extent of such tolerance; the specific positions of the variable regions which can be predictably modified and which regions are critical for maintaining antigen specificity and affinity for an epitope on one of the cell lines. Furthermore, given that the epitope of the antibody comprising the heavy chain variable region sequence of SEQ ID NOs:1 and the light chain variable region sequence of SEQ ID NOs: 3 is unknown and all that is required from the claims is that the variant antibody binds to one of the claimed cell lines it could not be ascertained whether the variant antibody binds to the same epitope as the unmodified antibody. Applicant's description as well as the cited art without more precise guidelines, amount to little more than "a starting point, a direction for further research." *Genentech*, 108 F.3d at 1366. *See also Calgene*, 188 F.3d at 1374 ("the teachings set forth in the specification provide no more than a 'plan' or 'invitation' for those of skill in the art to experiment practicing [the claimed invention]; they do not provide sufficient guidance or specificity as to how to execute that plan"); *National Recovery Technologies*, 166 F.3d at 1198 (stating that patent-in-suit "recognizes a specific need... and suggests a theoretical answer to that need. It provides a starting point from which one of skill in the art can perform further research in order to practice the claimed invention, but this is not adequate to constitute enablement"). The instant specification does not describe the claimed invention in terms that will "enable any person skilled in the art... to make and use" the invention commensurate in scope with the claims. At most, the specification will enable a person of ordinary skill in the art to attempt to discover how to practice the claimed invention.

As evidenced by the art of Rudikoff (cited by the examiner in the previous Office Action), even minor changes in the sequences of an antibody can have a dramatically effect antigen-binding function, particularly in the CDRs, thus, indicating the unpredictability in the art. The specification does not contain an example and the claimed invention is not disclosed in such a manner that one skilled in the art will be able to practice it without undue experimentation for reasons set forth above.

In view of the broad scope of the claims, the lack of guidance in the specification as it pertains to the claimed antibody variants, the absence of working examples, the lack of predictability of the art to which the invention pertains as evidenced by Rudikoff, undue experimentation would be required to practice the claimed antibody variants with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed antibody variants and absent working examples providing evidence which is reasonably predictive of the claimed antibody variants, commensurate in scope with the claims, the rejection is maintained.

35 USC § 102(a) rejections withdrawn

The rejection of claims 1, 2, 4 , 7-9, 11-16 and 54-65 under 35 U.S.C. 102(a) as being anticipated by Brändlein et al is withdrawn in view of the submission of the priority document.

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NEW REJECTION:

Claim Rejections - 35 USC § 112

Claims 76-78 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to

one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. THIS IS A NEW MATTER REJECTION.

There is no support in the specification as filed for a purified antibody, wherein the heavy chain or light chain variable region sequence has an insertion or deletion of one amino acid residue.

Applicants argue in the remarks on page 9, 2nd paragraph that the support for claims 76-78 can be found at page 13, line 23 to page 14, line 3, and at page 22, lines 17-22. The specification does have a general phrase asserting that "Any combination of deletions and substitutions can be made to arrive at the final construct". (page 22, lines 22-24). But there is no disclosure in the specification as filed for the specific phrase "wherein the heavy chain or light chain variable region sequence has an insertion or deletion of one amino acid residue".

Summary

Claims 1, 2, 4 , 7-9, 12-16 and 54-78 stand rejected.

Claim 11 is objected because it depends on the rejected base claim.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Halvorson, PhD whose telephone number is (571) 272-6539. The examiner can normally be reached on Monday through Friday from 8:30am to 5 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832. The fax phone number for this Art Unit is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic

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